REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 16, 20-23 and 31 will be active in the application subsequent to entry of this Amendment.

The claims have been amended in order to more particularly point out and distinctly claim that which applicants regard as their invention and to direct them to preferred aspects of the disclosure. The significance of these amendments and their basis in the description are given in the comments that follow.

The claims have been examined and a new reference applied, a U.S. patent to Lehmann. There are three prior art-based rejections, the first being of anticipation and limited to certain claims and the next two on "obviousness" directed to all of the previous claims based upon a combination of this newly cited Lehmann document in combination with a secondary reference. Applicant has amended his claims to specific subject matter that is in no way anticipated nor rendered obvious by the disclosures of the cited prior art.

The last paragraph on page 2 of the Official Action refers to "joint inventors". In fact, there is only a single inventor thus the assumptions and comments made in this passage are not relevant.

Claims 16, 17 and 25-31 were rejected as lacking novelty over the Lehmann reference (US 6143883). Claims 16 and 31 as above amended are novel. This document discloses a method for making low molecular weight, water soluble beta glucans and teaches that they are useful as immunomodulators in mammalian systems (column 2, lines 44 to 47). As the Examiner points out, Lehmann also goes on to state that as an immune system booster, the glucan is anticipated to boost wound healing (column 5, lines 29 to 31). Applicant notes however, that this effect is primarily linked to diabetes induced peripheral neuropathy, a disease not associated with fish, the main target of the present invention.

Lehmann makes repeated references to mammals and mammalian systems (as is clear even from the title of his patent) and it seems obscure therefore that fish and crustaceans are mentioned in the last paragraph in column 4 given that these are very definitely not mammalian. Moreover, it must be noted that discussion of fish and crustaceans is in the context of nutritional supplementation, i.e. in the diet of the organism.

In view therefore, of the objections raised and the Lehmann disclosure, the claims are above amended and are limited to exposure by water immersion treatment based on previous claim 25. Claim 16 is also limited to the treatment of fish, amphibians and invertebrates, i.e. exclusively non mammalian organisms, based on page 2, line 34 of the description. Finally, claim 16 is also limited to the use of a water soluble glucan. As will become apparent from the comments that follow, there is no point using a non water soluble glucan in a water bath. Previous claims 17 to 19 and 24-30 are deleted and claim 31 amended to reflect the changes in claim 16.

The disclosure of fish in Lehmann occurs in connection with the inclusion of beta-glucans in nutritional supplements. These are suggested for oral or parenteral application only in the column 4, line 43. There is no disclosure of fish immersion in a water bath of a beta-glucan in these passages or indeed in any other passage of Lehmann.

Note also that Lehmann's subsequent discussion of wound healing in column 5 is not made in connection with any specific mode of administration. The claims as above amended are directed to the specific combination of water bath immersion and wound healing using a soluble glucan in the treatment of non mammalian organisms.

The disclosure in column 5 of topical application is combined with a suitable carrier and applied as creams, lotions, salves and ointments. At no point is there a disclosure in Lehmann of the use of a water bath treatment. It is submitted that such treatment is not regarded as topical (and even if it is argued to be topical, there is still no explicit disclosure in Lehmann of the use of a water bath).

Attention is drawn to the instant specification where there is a clear distinction drawn between topical application, i.e. application of a cream/gel/ointment to a localized point on the skin to treat a condition, and immersion in a water bath where there is no "application" step and the whole surface of the organism is exposed to the beta-glucan. In particular, topical administration is discussed on page 4, line 26 of the specification separately from bath immersion on page 3.

The combination therefore of the application of:

1. wound healing
2. in fish, amphibians and invertebrates

3. with a water bath as a means of administering the compound

4. using a water soluble glucan

is not described in Lehmann. The majority of the Lehmann disclosure concerns mammalian applications and fish are not mammals. Bath immersion is not topical application and Lehmann does not teach bath immersion at all anyway.

The rejections stated in the second half of page 3 of the Official Action urging that the previously reviewed claims are "obvious" over a combination of Lehmann with the secondary reference is also traversed, in particular having regard to the amendments made to the claims presented above.

The combination of Lehmann with Hayen (WO 95/04467) is not one which is now relevant to the claims as Hayen's glucans are water **in**soluble. Attention is drawn to page 4, line 27 of Hayen where this is explicitly stated. The benefits of water soluble glucans are explained fully in the passages which follow. Hayen does not therefore teach the combination of a water soluble glucan and vitamins as required by claim 20. Hayen is concerned where the process where (water-insoluble) glucan is introduced into a food composition and is therefore administered orally. The present invention, as noted below, notes the incredible benefits of administering glucans via water bath immersion. The fact that vitamins in particular are also water soluble makes this bioavailable in solution too. There is no discussion in Hayen of the use of water immersion treatment in connection with fish.

The rejection stated on page 4 of the Official Action where Lehmann has been combined with another secondary reference is also equally flawed in many ways for the same reasons as the previous "obviousness" rejection is deficient.

The combination with the Rorstad document (EP '037) with Lehman (or vice versa) is more interesting (but actually also irrelevant) as it mentions in column 7 the possibility of "aqueous exposure". Rorstad is concerned with immunostimulation in certain fish and crustacea involving the administration of beta glucans thereto. Modes of administration include enteral, parenteral and via aqueous exposure and it is interesting to note that aqueous exposure is not regarded as topical in this document. The word "topical" is not used at all. Moreover, there is no definition of what constitutes "aqueous exposure". While that term would cover immersion it

would also cover, *inter alia*, drinking an aqueous composition of the glucan or spraying the fish with an aqueous glucan mixture neither of which would constitute immersion.

The claims of the present case specifically require **immersion** and this is not taught in Rorstad. Note also that Rorstad is not concerned with wound healing rather only with stimulating the immune system.

A further critical issue in Rorstad is that the glucans they use are M-glucans which are **not** water soluble (the same as Hayen's glucans). The claims cover particular proprietary glucans of the applicant which are supplied as microcomposites. Note the process for the manufacture of the glucans in claim 4 involves repeated water washing but isolation of the insoluble yeast component. On page 6, line 27, Rorstad explicitly confirms that the glucans he uses are **in**soluble.

In fact, insolubility is important for the glucans in Rorstad as they are given to the fish in their feed (or injected). If the glucan dissolved in water when the feed was placed in the water then the fish would not ingest it.

The applicant of the instant application has used M-glucan as described in Rorstad in an attempt to improve wound healing in fish by water immersion but this glucan has no beneficial effect in this mode of administration. The fact that the glucan does not dissolve in the water bath means the fish is not exposed to the glucan in a clinically significant dose.

The fact that Rorstad mentions aqueous exposure must therefore be read in conjunction with the knowledge that the glucan discussed is not water soluble. What therefore does aqueous exposure mean in that context? It certainly cannot mean immersion as it is pointless to immerse a fish in a water bath with an insoluble glucan.

The Examiner tries to combine Rorstad and Lehmann. Why however would the skilled person do so? Rorstad concerns aquatic animals and Lehmann concerns mammals, creatures with entirely different biology. The mention of fish in column 4, line 62 of Lehmann is, it is stressed, in the context of treatment by nutritional supplementation only and is obscure to say the least in the context of a document purporting to concern mammalian treatments.

It would be wrong to use the disclosure of "aqueous exposure" in Rorstad to argue that immersion is obvious for wound healing treatment in view of Lehmann. Remember that Rorstad discusses **in**soluble glucans only and cannot therefore consider immersion. Whatever aqueous

exposure means, immersion is not it. Note also that Lehmann concerns mammals. You do not immerse a horse in a water bath of beta glucan to treat wounds thereon.

All of the examples of Rorstad utilize injection of the necessary compound or incorporate it into a feed rather than any aqueous bath. The benefits of an aqueous bath are set out on page 3 of the application as filed and include the ability not only to improve wound healing and stimulate the immune system but also to improve the mucus quality in fish. The use of a bath has been found to reduce bacterial and pathogenic count and scrapings from the fish's mucus coating and these benefits are observed in the entire fish population not just in a small number of individuals. The benefits of a bath therefore are that while you might be trying to treat one or two individual fish with wound issues, you are simultaneously treating the entire fish population in a tank with a compound which is beneficial to their health. You are able to treat numerous animals simultaneously and the animals need not be aware that they have been treated. The benefits therefore of water immersion treatment are numerous.

Even setting up the necessary system is simple. All you need do is dissolve the necessary components in the water. There is no requirement to make a feed and incorporate into the feed the necessary glucans and then ensure that those glucans remain in a form which the fish actually eats.

Contrast also water immersion to topical application to a fish. To topically apply an agent, firstly of course, the fish needs to be caught. Unlike a mammal, fish release cortisol when captured as an adverse reaction to being caught. The release of cortisol has an adverse effect on the success of any treatment. Moreover, higher levels of cortisol subsist for days in fish making veterinary outcome uncertain for topical application.

The next problem is actually applying the topical formulation. That involves touching the skin of the fish, which is undesirable, and must also involve a formulation that sticks to the skin. The formulation cannot be water soluble as it would just wash off but must adhere to the fish skin. Such a formulation is a tricky material to manufacture. Topical application can even result in skin damage resultant from the application procedure, and subsequent limitation of wound healing rates. Furthermore, if the wound is on the gills of the fish, topical application of a medicine results in the fish dying. Immersion allows gill treatment to occur.

A further problem with topical creams is how they effect the water. Mammals live in the air where the environment is standard. Fish live in water which has different levels of salinity and pH and so on. Each fish species tends to live in a specific environment and the addition of a topical medicine can change the osmolality of the water. That again has adverse effects of fish health. Each cream should therefore be tailored to not upset the critical balance of pH and salinity etc for a particular species.

There are therefore all kinds of problems using topical medicines which the present invention solves. The use therefore of water bath immersion has the following benefits.

1. The whole body surface can be treated when the environment is used as the product carrier. In fish this also relates to the delicate structures such as the gills to which topical creams, pastes, gels etc cannot be applied without potential harm the animal due to interference with respiration and ion exchange necessary for osmoregulation (chloride and potassium pumps are on the surface of the gill and would fail if covered by a carrier).

2. Treatment of the whole body surface is important in control of the surface immunity. Oral use does not provide the same clinical response as environmental therapy.

3. In fish and some amphibians, the gills are exposed allowing both surface activity and systemic uptake. The skin also can act as an uptake system and immersion of the whole animal is much safer and treats the whole body surface allowing higher systemic levels to be achieved.

4. Its environmental use allows the environmental level of the active to be maintained and unaffected by metabolic or chemical degradation. Creams and gels do not typically adhere well to the mucous coat.

5. Large groups of animals can be treated in this way, such as its use in preventative medicine regimes for ornamental fish, farmed fish, amphibians and invertebrates. Whole tanks can be treated without contact with the patient. This would not be possible with topical agents.

Applicant wishes to further illustrate the effects of the present invention visually in the five sheets of materials attached to this response. The pictures show the wound healing in a sailfin over a period of 233 days. It is expected that this information will be presented in the form of an evidentiary declaration under 37 CFR §1.132 in the near future to place this evidence in proper formal order.

Attached are five separate images made days 4, 5, 9, 36 (labelled) and 233 (no number on this image) after treatment. These are taken from a clinical case treated with potentiated soluble glucans according to the invention. Application of therapy was by an immersion of the patient in an aqueous environment containing 1ml/liter of a 2% solution of water soluble 1-3, 1-6 betaglucans containing a vitamin composition for a bath treatment of 1-3 hours duration on a daily treatment basis. The animal following each bath application was returned to a holding tank. The composition and treatment methodology has a remarkable effect on accelerating wound healing by application in the aqueous environment, and has an anti-inflammatory activity as will be seen from these images.

The images are in color and it is counsel's understanding that the PTO's scanning devices will convert this into a black and white image. For the examiner's convenience counsel will forward these images in color to the examiner via e-mail at a later date when she returns to the office.

To summarize, the use of the claimed method avoids any direct contact with the animal such as would occur by use of a topical product - such topical therapy would require restraint (which may require sedation/anaesthesia) which can increase the risk of further wound damage, disruption of the surface of the wound and reduce the treatment efficacy due to the long term cortisol release known to occur following stress exposure in aquatic animals.

Aquatic animals such as fish and amphibians have a mucous structure which is vital for the wound healing process. Chemicals used for the formation of creams and gels can by virtue of their chemical structure, interfere with wound healing and they do not allow the correct regeneration of the mucopolysaccharides at the wound margins. This can result in a reduction in immune cell activity, including macrophage activity, at the wound site. The pressure of application can also damage this delicate structure. Additionally, topical products applied directly to the skin surface of aquatic animals can lead to an alteration in local osmoregulation which in turn may lead to local skin pathology and negative systemic effects. Using the product in the aqueous environment avoids these problems and provides an accelerated rate of wound healing. Application via the environment allows the vitamins and glucans to be directly bioavailable at the cell membranes in the wound site and body surface which provides an increased efficacy compared to the oral form.

Systemic activity can occur via its use in the environment, for example the product can enter the systemic circulation via the gills in fish.

The combination of the Lehmann patent with the additional reference(s) do not render obvious the claimed invention because all limitations of independent claims 16 and 31 are not fairly taught or suggested in the cited patents. Moreover, claims depending from those independent claims are also not made obvious by the documents because the limitations of an independent claim are incorporated in their dependent claims. M.P.E.P. § 2143.03 citing *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988).

Withdrawal of the Section 102 and 103 rejections is requested because the claimed invention is novel and would not have been obvious to the ordinarily skilled artisan at the time Applicant made his invention.

Having responded to all of the pending rejections contained in the Office Action, Applicant submits that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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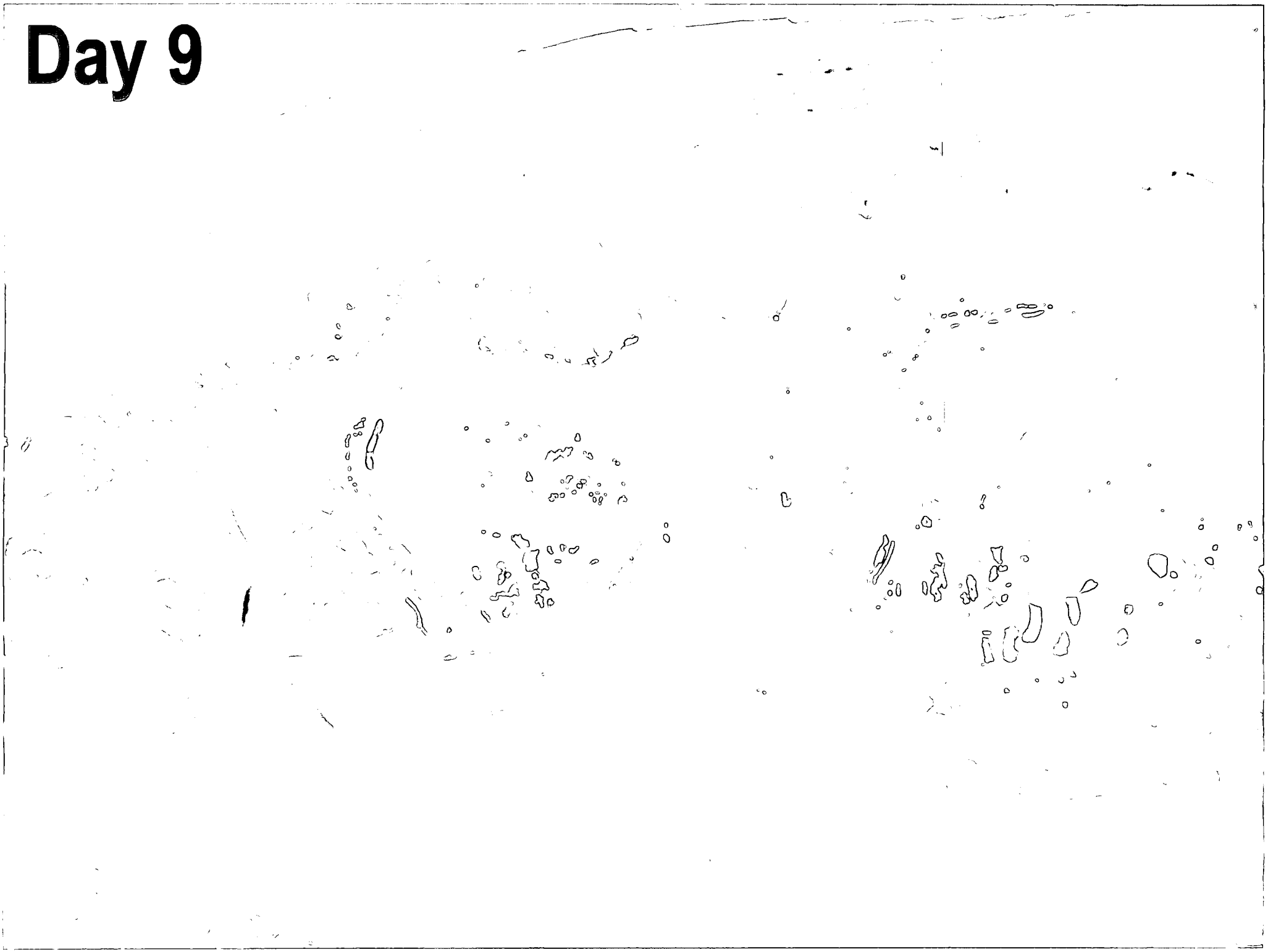
Day 5

Day 9



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